

[CASE REPORT]

Usefulness of Capsule Endoscopy and Double-balloon Enteroscopy for the Diagnosis of Multiple Carcinoid Tumors in the Small Intestine: Case Reports and a Literature Review

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Abstract:

The incidence of carcinoid tumor in the small intestine is increasing; however, its preoperative diagnosis is difficult. We recently experienced three cases of multiple carcinoid tumors in the small intestine successfully detected using capsule endoscopy (CE), followed by a pathological diagnosis using double-balloon enteroscopy (DBE). To diagnose multiple carcinoid in the small intestine appropriately, we reviewed the information of five cases reported to date along with our three recent cases. The literature review demonstrated that CE and DBE are useful for detecting and diagnosing small intestinal carcinoids and tumor multiplicity, which aids in determining the appropriate resection range.

Key words: carcinoid tumors, capsule endoscopy, double-balloon enteroscopy, octreotide scan

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Introduction

Tumors in the small intestine are rare, accounting for less than 5% of all gastrointestinal neoplasms (1). However, the incidence of small intestinal malignancies is increasing considerably, due mainly to the increased incidence of carcinoid tumors (1). Currently, carcinoid tumors account for 20% to 30% of tumors and are the second-most frequently diagnosed cancer in the small bowel (1). They are frequently diagnosed in the ileum, with a 20-40% incidence rate among tumors in the small intestine (1, 2). While carcinoid tumor is found frequently in the small intestine in the US (20-30% of cases), it is found there in approximately 5% of cases in Japan, indicating a difference in frequency of this disease among countries (1). Based on the World Health Organization (WHO) classification, carcinoid tumors have been classified into neuroendocrine tumors (NETs) G1, NET G2, and neuroendocrine carcinomas (NECs) according to their malignant potential and histological analyses (WHO classification 2010).

One of the major clinical characteristics of intestinal car-

cinoid tumors is its multiplicity, showing a diffuse distribution or overlapping tumors in 20-30% of patients (1, 3). The endoscopic findings include submucosal tumor-like lesions, depressive lesions on top of the tumor, capillary vascular dilatation, and villous atrophy, reflecting the fact that carcinoid tumors originate from epithelial tissue. However, because of the lack of specific signs, symptoms, and definitive preoperative diagnostic tests, the preoperative diagnosis of carcinoid tumors is difficult. Indeed, the accurate preoperative diagnosis rate is approximately 5%, and carcinoids of the small intestine are often diagnosed incidentally upon resection of the small intestine for obstruction or during exploration of the small intestine to find a primary lesion of metastatic tumors.

Given that the increased incidence of small bowel tumors is predominantly due to the increased incidence of carcinoid tumors and because surgical resection is the standard procedure for the treatment (1), the development of an effective method for detecting and diagnosing carcinoid tumors is essential. To this end, we explored the efficacy of capsule endoscopy (CE) and double-balloon enteroscopy (DBE) in terms of their sensitivity compared with an octreotide scan

by evaluating the course of recent cases of multiple small intestinal carcinoid tumor and summarizing the information on the cases reported to date in which CE and DBE were applied (Table).

Case Reports

The details of the courses of our three recently experienced cases (Cases 1 to 3) have been summarized below, while the details of the five previously reported cases (Cases 4 to 8) are summarized in Table.

Case 1

A 60-year-old woman was referred to our hospital with symptoms of melena and anemia. She showed mild anemia with a hemoglobin level of 9.6 mg/dL, and neither tumor markers nor gastrointestinal hormones were elevated. Computed tomography (CT) showed no significant findings. CE (PillCam SB; GIVEN, Yokneam, Israel) showed multiple submucosal tumor (SMT)-like lesions in the ileum. To determine the distribution of the tumors and to diagnose the metastatic lesions, an octreotide scan was performed (Fig. 1a). The scan detected only one major tumor in the intestine (Fig. 1b-g) and potential lymph node metastases around the tumor. Therefore, DBE was performed both transorally and transanally; as a result, 13 tumors, approximately 5 mm in size, were detected, showing SMT-like lesions with a depressive pattern in the tumors, including those detected using the octreotide scan (Fig. 1b).

A tissue biopsy showed the following: chromogranin A (Fig. 1c), synaptophysin (Fig. 1d), and CD56 (Fig. 1e) positively stained tumor cells, with <1% of tumor cells staining positive for Ki-67 (Fig. 1f), leading to a diagnosis of carcinoid tumor. In addition, DBE revealed multiple tumors in the intestine initially detected by CE (Fig. 2a) that had been unable to be diagnosed with the octreotide scan (Fig. 2b, c).

Based on site mapping of tumor localization, partial resection of the intestine confirmed by endoscopy during surgery and lymphadenectomy were performed. Ultimately, 15 tumors in the small intestine were diagnosed in the resected tissues histologically, including 2 small tumors undetectable by preoperative examinations using an octreotide scan, CE, and DBE. The lymph node metastases were successfully removed, and as of one year after the surgery, the patient remains disease-free.

Case 2

A 71-year-old man with bloody stool underwent esophagogastroduodenoscopy and colonoscopy, and since no bleeding point was detected, we performed CE and detected an ulcerative lesion in the proximal ileum. DBE was carried out transanally and reconfirmed the presence of two tumors in the ileum. Biopsies taken from these lesions showed a low-grade neuroendocrine tumor with characteristics consistent with a carcinoid tumor. The patient showed no metastases in a series of imaging examinations and subsequently

underwent partial small bowel resection. Three other tumors were discovered in the ileum by intraoperative endoscopy, and the resected specimen showed tumors of 4-18 mm along with lymph node metastases. During the six-year follow-up period, the patient showed no recurrence or metastasis.

Case 3

A 76-year-old man underwent CT for screening, and 2 slightly enhanced nodules in the small bowel were suspected. CE showed eight tumors, and transanal DBE showed three SMT-like lesions in the ileum. Biopsies taken from these lesions showed carcinoid tumor. No tumors were discovered in the rest of the intestine by intraoperative endoscopy, and the resected specimen showed a 60-cm-long ileum with 15 tumors with a diameter of 2-15 mm as well as 2 lymph node metastases. As of eight years after the surgery, the patient remains disease-free.

Discussion

Carcinoid is a common malignancy in the small intestine and accounts for approximately one-third of all small intestinal lesions (4). In addition, the incidence of these tumors in the small intestine is increasing (1), and most are located in the terminal part of the ileum. They often involve metastases to regional lymph nodes and then to other organs, such as the liver. (5). Magnetic resonance imaging (MRI) and CT are useful for diagnosing the location of these tumors (6). However, small intestinal carcinoid tumors have been reported to show multiplicity in 20-30% of patients (3), and Bellutti et al. suggested that, in such cases, intraoperative endoscopy is a potential gold-standard diagnostic for multiple tumors (7). To determine the appropriate surgical procedure, a preoperative diagnosis of tumor multiplicity is essential; therefore, the development of a method for diagnosing multiplicity and locations of tumors is essential. Octreotide scanning has been used to screen for potential metastatic lesions and multiplicity; however, as the signal is dependent on the expression of the receptor protein, its sensitivity and specificity for detecting even the primary lesion is unsatisfactory (8). Therefore, combination of imaging modalities with endoscopic procedures for pathological diagnosis is necessary (8).

Recent developments in CE have increased the rate of tumor detection in the small intestine, and subsequent DBE has been used to detect, diagnose, and perform biopsies of lesions in the small intestine (4, 9). This has achieved a preoperative diagnostic rate of 80% in patients (5, 7, 9, 10). Our literature review revealed that, although multiple small intestinal carcinoid tumors have been reported, only five cases were directly diagnosed by DBE. Therefore, we carefully reviewed these cases and summarized their findings in Table, including the findings of our three recently encountered cases. The average age of the total patients was 67.4 years (range 48-77), and the ratio of men to women was 5: 3. Seven out of the eight patients presented with melena,

Table. Summary of Cases Reported.

Case (No)	Reference	Age (yrs)	Gender	Symptoms	Localization	Maximum size (mm)	Computed tomography	Number of Carcinoid Tumors Detected					Metastasis			
								Octreotide scan	Capsule endoscopy	Double- balloon enteroscopy (O, transoral; A, transanal)	Intraoperative diagnosis	Histological diagnosis	Treatment	Recurrence free period	Lymph nodes	Distant
1	Our case	60	Female	melena	ileum	7	n.p.	1	5	13 (O and A)	N/A	15	partial resection of the intestine, lymphadenectomy	1 year	+	-
2	Our case	71	Male	melena	ileum	18	wall thickness in ileum	N/A	2	2 (A)	5	5	partial resection of the intestine, lymphadenectomy	6 years	+	-
3	Our case	76	Male	none	ileum	15	lymphadenopathy	N/A	8	3 (A)	multiple	15	partial resection of the intestine, lymphadenectomy	8 years	+	-
4	(3)	48	Male	melena, anemia	ileum	10	n.p.	N/A	N/A	5 (A)	5	5	partial resection of the intestine, lymphadenectomy	9 months	+	-
5	(11)	77	Female	melena	ileum	15	n.p.	N/A	N/A	3 (O and A)	multiple	12	partial resection of the intestine, lymphadenectomy	2 years	+	-
6	(7)	68	Male	melena	ileum	30	N/A	1	1	2 (O and A)	unknown	2	partial resection of the intestine, lymphadenectomy	N/A	unknown	unknown
7	(12)	64	Male	melena, anemia	jejunum & ileum	N/A	n.p.	1	multiple	multiple (A)	N/A	unknown	partial resection of the intestine	N/A	unknown	-
8	(13)	75	Female	melena, anemia	jejunum & ileum	14	n.p.	N/A	N/A	3 (O and A)	N/A	3	partial resection of the intestine, lymphadenectomy	1.5 years	-	-

N/A: data not available, n.p.: no particular findings

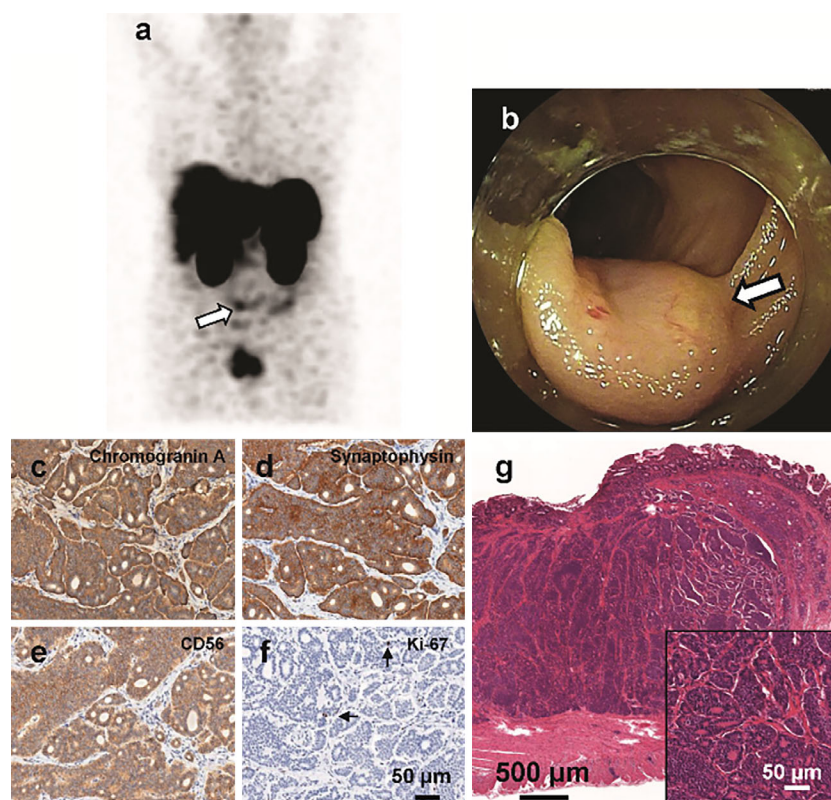


Figure 1. Carcinoid tumor detected with octreotide scan. a: Image of the octreotide scan. The white arrow indicates the suspected tumor. b: The tumor confirmed with double-balloon endoscopy. The white arrow indicates the tumor. c-f: Immunohistochemical staining of the tumor. c: Chromogranin A staining, d: Synaptophysin staining, e: CD56 staining, f: Ki-67 staining. Black arrows indicate positively stained cells. g: Hematoxylin and Eosin staining of the tumor.

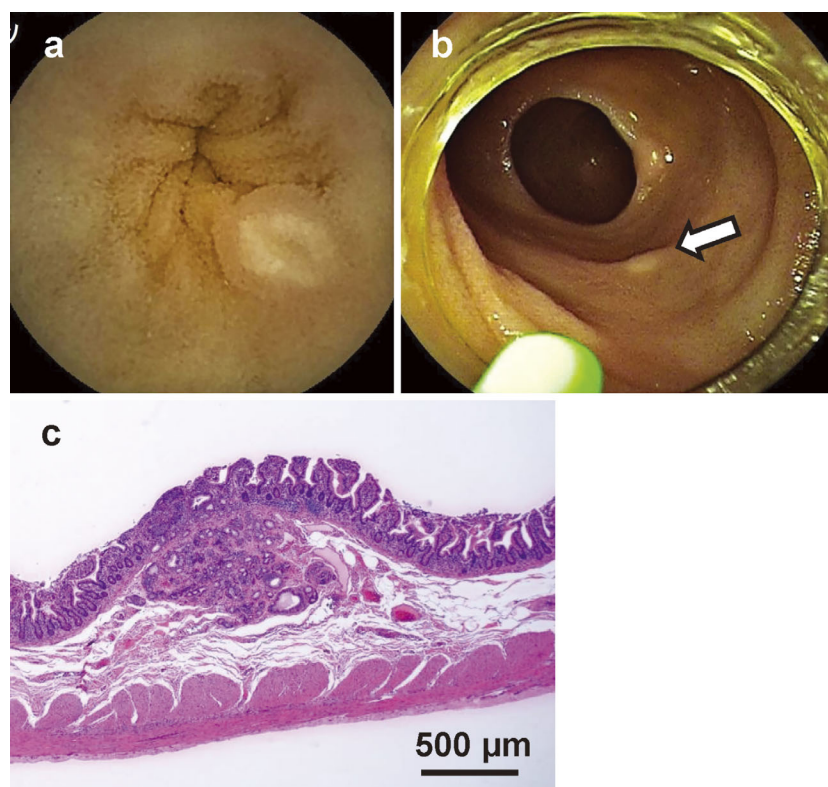


Figure 2. Carcinoid tumor detected with capsule endoscopy (CE). a: Image obtained on capsule endoscopy. b: The tumor confirmed with double-balloon endoscopy (DBE). The white arrow indicates the tumor. c: Hematoxylin and Eosin staining of the tumor.

and four presented with anemia. While carcinoid syndrome reportedly occurs in approximately 20% of patients with small bowel carcinoid (5), none of the cases summarized in Table showed carcinoid syndrome. Tumors were detected in the ileum in six cases and at the ileum/jejunum in two cases. The diameter ranged from 7 to 30 mm, and number of tumors ranged from 2 to 15. Although CT enterography was performed in one case and an octreotide scan was performed in three cases, the location and multiplicity of the carcinoid tumors were difficult to diagnose using these modalities. CE was performed in five cases, and DBE was performed in all cases; no complications associated with either were observed. DBE showed a better detection of tumor multiplicity than octreotide scan (Table), and CE detected more tumors than DBE (Case 3). However, the entire intestine was not observed in six out of eight cases. Given the invasiveness of the examinations, it might be best to start with CE followed by DBE to perform histological analyses when small intestinal tumors are detected. In all of the cases summarized, partial resection of the small intestine and lymph node dissection were performed.

Based on the findings of our cases as well as the reviewed cases, although CE is useful for detecting multiple lesions in the small intestine in a low-invasive manner, DBE is necessary for determining the precise location, number of tumors, and pathological diagnosis as well as for diagnosing multiple carcinoid tumors in the small intestine. The data obtained from DBE and the tumor position marking on the upon DBE help determine the lesion and length of the small intestine to be resected. Therefore, both transoral and transanal DBE are essential for precisely planning resection and preventing small bowel syndrome. The lower sensitivity with CT enterography and octreotide scan than with DBE was probably because of the tumor size and the low or high level of somatostatin receptors. Overall, our review showed the usefulness of CE and DBE for detecting and diagnosing small intestinal carcinoid preoperatively, leading to the determination of an appropriate resection range. The information summarized in this paper will help physicians diagnose small intestinal carcinoid.

The study was reviewed and approved by the Institutional Review Board of Niigata University.

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

The authors state that they have no Conflict of Interest (COI).

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